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BEFORE THE BOARD OF APPEALS AND INTERFERENCES
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Tessier-Lavigne et al.	Group Art Unit: 1631
Serial No. 09/273,098	Examiner: Allen, M.
Filed: March 19, 1999	Attorney Docket No. UC99-244-2
For: *Compositions for Promoting Nerve Regeneration*	CERTIFICATE OF MAILING I hereby certify that this corr. is being deposited with the US Postal Service as First Class Mail in an envelope addressed to the Comm. for Patents, Washington, D.C. 20231 on February 23, 2001. Signed _____ Richard Osman

BRIEF ON APPEAL

The Commissioner of Patents
Washington, D.C. 20231

Dear Commissioner:

This is an appeal from the 12/6/00 rejection of claims 1-4 and 6, 8-9, 12-16, 19-24.

REAL PARTY IN INTEREST

The real party in interest is the Regents of the University of California, the assignee of this patent application.

RELATED APPEALS AND INTERFERENCES

Appellants are unaware of any related appeals or interferences.

STATUS OF THE CLAIMS

Claims 1-4 and 6, 8-26 are pending; claims 1-4 and 6, 8-9, 12-16, 19-24 are subject to this appeal. The pending, duly limited group III and IV method claims 10, 11, 17, 18, 25 and 26 are subject to a pending request for rejoinder. The remaining claim 7 is a duplicate of subject

claim 14 and will be canceled upon resolution of this appeal.

STATUS OF THE AMENDMENTS

All Amendments are believed to be properly before the Board.

SUMMARY OF THE INVENTION

Many neurons in both vertebrates and invertebrates innervate multiple targets by sprouting secondary axon collaterals (or branches) from a primary axon shaft. To identify molecular regulators of axon branch initiation or extension (Tessier-Lavigne and Goodman 1996, Science 274, 1123-33.), Appellants studied the growth of single sensory axons in an in vitro collagen assay system, and identified an activity in extracts of embryonic spinal cord and of postnatal and adult brain that promotes the elongation and formation of extensive branches by these axons. Using biochemical purification of the activity from calf brain extracts, Appellants identified an amino-terminal fragment of Slit-2 as the main active component (see, Wang et al., 1999, Cell 96, 771-784). Appellants disclose that N-terminal fragments of Slit proteins (see Kidd et al., 1999, Cell 96, 785-794; Brose et al., 1999, Cell 96, 795-806; and Li et al., 1999, Cell 96, 807-818), can function as positive regulators of axon collateral formation during the establishment or remodeling of neural circuits and that the activity of these proteins can synergize in vitro and in vivo with other neurotrophic agents like NGF. Appellants report that Slit-N proteins can function to regulate axon collateralization not just during the initial development of axonal connections, but also during normal plastic rearrangements of neural connections that occur in the adult nervous system. Following injury to the spinal cord, Slit-N proteins can induce regeneration by stimulating collateralization of axons from fiber tracts into the CNS gray matter, and/or axon regrowth in an inhibitory environment, to help alleviate the paralysis that accompanies injury to fiber tracts. Specification, p.1, line 15 - p.2, line 4.

A "minireview" of the foregoing Slit technical literature has recently been published (Van Vactor et al., 1999, Neuron 22, 649-652) and to the extent the Board wishes an overview of the subject matter, a copy is appended hereto.

The claimed invention is directed to natural sequence Slit-N polypeptide, and particularly

wherein the natural sequence Slit-N polypeptide is selected from the group consisting of an hSlit-1-N, an hSlit-2-N and an hSlit-3-N polypeptide. In more particular embodiments, the natural sequence Slit polypeptide is contained in a pharmaceutical composition or made by expressing a Slit protein in a cell, whereby the Slit protein is proteolytically processed to form the Slit-N polypeptide. Pending claims 1-4, 12-13, 19-21.

The invention also encompasses a pharmaceutical composition comprising a therapeutically effective amount of a subject natural sequence Slit-N polypeptide and a pharmaceutically acceptable excipient, and optionally further comprising a therapeutically effective amount of a neuroactive agent other than the Slit-N polypeptide, such as NGF. Pending claims 6, 8-9, 14-16, 22-24.

ISSUES

I. WHETHER CLAIMS 1-4, 6, 12-14 and 19-22 ARE PATENTABLE UNDER THE JUDICIALLY CREATED DOCTRINE OF OBVIOUSNESS-TYPE DOUBLE PATENTING OVER CLAIMS 1-12 OF US PATENT NO. 6,046,015.

II. WHETHER CLAIMS 1-4, 6, 8-9, 12-16 and 19-24 ARE PATENTABLE UNDER 35USC112, FIRST PARAGRAPH (WRITTEN DESCRIPTION).

III. WHETHER CLAIMS 3, 6, 8-9, 12, 14-16, 20 AND 22-24 ARE PATENTABLE UNDER 35USC112, SECOND PARAGRAPH.

IV. WHETHER CLAIMS 1-4, 6, 8, 12-15 AND 19-23 ARE PATENTABLE UNDER 35USC102(e) IN VIEW OF US PATENT NO. 6,046,015.

GROUPING OF THE CLAIMS

For Issue I, claims 1-3, 6, 12-14 and 19-22 shall be considered as a group; claim 4 shall be considered separately.

For Issue II, claims 1, 3, 6, 8, 9 shall be considered together as a group; claims 2, 12, 13, 14, 15, 16 shall be considered as a group; claims 19, 20, 21, 22, 23, 24 shall be considered as a group; claim 4 shall be considered separately.

For Issue III, claim 3 shall be considered separately; claim 20 shall be considered separately, and claims, 6, 8-9, 12, 14-16, and 22-24 shall be considered as a group.

For Issue IV, claims 1-3, 6, 8, 12-15 and 19-23 shall be considered together as a group; claim 4 shall be considered separately.

ARGUMENT

I. CLAIMS 1-4, 6, 12-14 and 19-22 ARE PATENTABLE UNDER THE JUDICIALLY CREATED DOCTRINE OF OBVIOUSNESS-TYPE DOUBLE PATENTING OVER CLAIMS 1-12 OF US PATENT NO. 6,046,015.

(i) Claims 1-3, 6, 12-14 and 19-22.

First, it is unclear to Appellants if this double patenting rejection is consistent or proper in this context, as the Examiner has also cited the same patent as anticipatory prior art under 35USC102(e). If the inventions are purported to be the same invention (as per the allegation under 102(e)), this rejection should be statutory; if they are purported to not be the same invention (as per this obvious-type double patenting rejection), the anticipation rejection fails. Furthermore, the judicial justification for the doctrine of obviousness-type double patenting does not appear to sustain where the cited art is already citable prior art under 102(e). In any event, the analysis is essentially the same as would be a rejection under 35UCS103/102(e), so to expedite Board review, we construe the rejection as such.

The claimed invention is patentably distinct from that claimed in Goodman et al. (US Patent No.6,046,015). The cited patent describes and claims slit fragments generally, but there is no mention of, no suggestion of, nor claims to natural sequence Slit-N polypeptides as claimed herein. While the Action does not provide a prima facie case under double patenting or prior art (35UCS103/35USC102(e), Appellants have of record affirmative evidence in the form of an expert Declaration (copy enclosed) of Dr. Goodman himself, confirming that the cited art does not teach or suggest the claimed natural sequence Slit-N polypeptides or methods of use. Accordingly, the uncontroverted evidence of record demonstrates that the claimed invention is neither anticipated nor suggested by the cited Goodman et al. reference. Absent a prior art disclosure teaching or suggesting the subject natural sequence Slit-N polypeptides, the claims are clear of any statutory or judicially created double patenting objection and in compliance with 35USC103/35USC102(e).

In fact, the claims are limited to subject matter providing wholly unexpected results. As

explained below (written description analysis) the subject natural sequence Slit-N polypeptides necessarily and by definition stimulate elongation and branching of neuronal axons. In contrast, prior to the present disclosure, the art taught that Slit proteins were chemorepellents (see Brose et al., supra; Kidd et al., supra, Wang et al., supra); there is no prior art suggestion of the surprising finding, disclosed herein, that natural N-terminal domains of these Slit polypeptides exist or that such domains "function as positive regulators of axon collateral formation during the establishment or remodeling of neural circuits and that the activity of these proteins can synergize in vitro and in vivo with other neurotrophic agents like NGF..."; Specification at p.1., line 25 - p.2, line 4; Goodman Declaration, supra, p.2, lines 3-8.

(ii) Claim 4.

Claim 4 is specifically limited to a natural sequence Slit-N polypeptide made by expressing a Slit protein in a cell, whereby the Slit protein is proteolytically processed to form the Slit-N polypeptide. Limited by the recited process, the claim distinguishes Slit-N polypeptides directly expressed (Specification, p.3, lines 10-19). There is no claim in Goodman et al. directed to a natural sequence Slit-N polypeptide made by expressing a Slit protein in a cell, whereby the Slit protein is proteolytically processed to form the Slit-N polypeptide. Appellants are unaware of any settled legal authority holding that a product-by-process claim is not limited to a product made by the recited process.

II. WHETHER CLAIMS 1-4, 6, 8-9, 12-16 and 19-24 ARE PATENTABLE UNDER 35USC112, FIRST PARAGRAPH (WRITTEN DESCRIPTION).

(i) Claims 1, 3, 6, 8, 9.

Slit-N polypeptides, and particularly natural sequence Slit-N polypeptides, are consistently defined. Natural sequence Slit-N polypeptides are known in the art to refer to a class of proteins naturally produced as N-terminal proteolytic fragments of Slit polypeptides (Specification, p.3, lines 6-8; p.7, line 32 - p.8, line 4; Wang et al., supra, at 776-784; Van Vactor et al., supra) and which stimulate elongation and branching of neuronal axons (Specification, p.1, line 23 - p.2, line 4; Wang et al., supra; Van Vactor et al, supra). Residue boundaries of natural

sequence Slit-N polypeptides are readily determined (Specification, p.3, lines 2-29) and exemplified, e.g. hSlit-2-N is bound by Met1 and Arg1117 of hSlit-2; dSlit-2-N is bound by Met1 and Gln1111 of dSlit-2 (Specification, p.3, lines 26-27).

Slit proteins themselves are an art recognized class of neuroactive proteins; diverse and numerous examples of Slit proteins were well known in the art as of March 19, 1999. For example, Brose et al. (supra at p.796) describe human (h) Slit polypeptides: hSlit-1, hSlit-2, hSlit-3; rat (r) Slit polypeptides: rSlit-1, rSlit-2, rSlit-3; as well as Slit polypeptides from Drosophila and C. elegans. In fact, we have of record scientific publications from a variety of research laboratories across the country that all use the same Slit and Slit-N nomenclature to describe the same family of proteins, and do so without sequence recitations. Those skilled in the art determine how much description they need and their art-recognized adoption and consistent usage of the technical terms Slit and Slit-N demonstrates that the terms are sufficient to relate possession to those skilled in the art. Appellants need not and should not burden the public with needless amino acid sequence recitations of well-known proteins.

Large proteins like Slit are often proteolytically cleaved in the body to form two separate chains. For example, many tyrosine kinases and receptors are expressed as a large polypeptide and then proteolytically cleaved into two chains that frequently associate non-covalently. These are often called alpha and beta chains. Appellants identified a similar phenomenon with Slit - it too is cleaved into two fragments, designated Slit-N and Slit-C (Specification, p.3, lines 17-18; Wang et al., supra at p.776; Van Vactor et al., supra, paragraph bridging p.651 and 652). Though there is no prima facie case to the contrary, for good measure, Appellants have of record affirmative evidence in the form of an expert Declaration (copy enclosed) from one of the world's foremost authorities in the field confirming that the disclosure clearly conveys to those skilled in the art that Appellants had possession of the invention as claimed.

The 5/2/00 and 12/6/00 Actions rely on no more than unsubstantiated and/or inaccurate allegations. In response, we note that Slit-N polypeptides are structurally and functionally defined and described. Slit-N polypeptides are functionally limited and necessarily stimulate elongation and branching of neuronal axons (e.g. Specification, p.2, lines 9-10). Arbitrary Slit fragments and full length Slit proteins are clearly not encompassed by natural sequence Slit-N

polypeptides. The activity of Slit-N polypeptides is necessarily distinct from the chemorepellant activity associated with Slit proteins (see also, Specification, p.8, line 8). Appellants indeed intend to limit their claims to natural sequence Slit-N polypeptides. Our claims do not encompass Slit polypeptides that are of non-natural sequence. The specification indeed describes non-natural sequence Slit-N polypeptides – however, these are not encompassed by our claims. Slit-N polypeptides have indeed been described - in fact, they are well known in the art in a variety of species (supra.). Slit is indeed a secreted protein and as such, is initially translated with a signal sequence that is cleaved off before the protein is secreted and subject to further processing - hence a *natural sequence Slit-N polypeptide* with a signal or leader sequence does not exist.

In any event, the Actions' speculative discussions are offered without support and do not appear to bear on the present subject matter nor claims. The Examiner is certainly entitled to establish herself as an expert and provide rebuttal evidence. However, as presently presented, her arguments are not evidence nor is there any evidence of record suggesting any basis by which the Examiner can attest to the mind of one of ordinary skill in the art. The uncontroverted evidence of record establishes that the claims are in compliance with the written description requirement of 35USC112, first paragraph.

(ii) Claims 2, 12, 13, 14, 15, 16.

Claims 2, 12, 13, 14, 15 and 16 are specifically limited to wherein the Slit-N polypeptide is selected from the group consisting of an hSlit-1-N, an hSlit-2-N and an hSlit-3-N polypeptide. These define the Slit-N chains of three specific and defined human proteins, hSlit-1, hSlit-2 and hSlit3 (see Brose et al., supra, at p.796). Hence, this embodiment is even more specifically described.

(iii) Claims 19, 20, 21, 22, 23, 24.

Claims 19, 20, 21, 22, 23 and 24 are specifically limited to wherein the Slit-N polypeptide is hSlit-2-N. Human Slit-2-N defines the Slit-N chain of a specific and defined human protein, hSlit-2. In fact, the specification even recites the amino acid boundaries of this particular Slit-N

species (Specification, p.3, line 26). Hence, this embodiment is even more specifically described.

(iv) Claim 4.

Claim 4 is specifically limited to a natural sequence Slit-N polypeptide made by expressing a Slit protein in a cell, whereby the Slit protein is proteolytically processed to form the Slit-N polypeptide. This process for making a natural sequence Slit-N polypeptide is described, inter alia, on p.3, lines 6-9 and on p.7, line 32 - p.8, line 4. Limited by the recited process, the claim distinguishes Slit-N polypeptides directly expressed (Specification, p.3, lines 10-19). Appellants are unaware of any settled legal authority holding that a product-by-process claim is not limited to a product made by the recited process.

III. WHETHER CLAIMS 3, 6, 8-9, 12, 14-16, 20 AND 22-24 ARE PATENTABLE UNDER 35USC112, SECOND PARAGRAPH.

(i) Claim 3.

Claim 3 is submitted to be clear in further limiting the recited polypeptide to be contained in a pharmaceutical composition. Such compositions are thoroughly described and exemplified, e.g. p.6, line 20 - p.7, line 26. A "pharmaceutical composition" need not be in dosage form so need not be quantitatively restricted to a therapeutically suitable amount for any particular use.

(ii) Claims 6, 8-9, 12, 14-16, 22-24.

Claims 6, 8-9, 12, 14-16 and 22-24 are submitted to be clear in reciting a therapeutically effective amount (in reference to the recited Slit-N polypeptide and the recited neuroactive agent). Such amounts are described and exemplified on p.6, lines 16 - p.7, line 26; p.8, lines 21-25; p.11, lines 10-14. The desired therapeutic effect is to promote nerve regeneration and treat neuropathy, which is the exclusive subject of this invention; see, e.g. title; field of the invention; p.1, line 25 - p.2, line 4; p.2, line 27 - p.3, line 3, etc.

(iii) Claim 20.

Claim 20 contains the objected to limitation of claim 3 and that of claims 6, 8-9, 12, 14-16, 22-24, as addressed above. Accordingly, claim 20 is submitted to be clear for the reasons explained in both foregoing paragraphs.

IV. WHETHER CLAIMS 1-4, 6, 8, 12-15 AND 19-23 ARE PATENTABLE UNDER 35USC102(e).

(i) Claims 1-3, 6, 8, 12-15 and 19-23.

Goodman et al. (US Patent No.6,046,015) describes and claims slit fragments generally, but there is no mention or suggestion of natural sequence Slit-N polypeptides. While the Action does not provide a prima facie case under either 35UCS102(e) or 35UCS103, Appellants have of record affirmative evidence in the form of an expert Declaration, confirming that the cited art does not teach or suggest the claimed natural sequence Slit-N polypeptides or methods of use. Accordingly, the uncontroverted evidence of record demonstrates that the claimed invention is neither anticipated nor suggested by the cited Goodman et al. reference. Absent a prior art disclosure teaching or suggesting the subject natural sequence Slit-N polypeptides, the claims are in compliance with 35USC102(e) and 103.

(ii) Claim 4.

Claim 4 is specifically limited to a natural sequence Slit-N polypeptide made by expressing a Slit protein in a cell, whereby the Slit protein is proteolytically processed to form the Slit-N polypeptide. Limited by the recited process, the claim distinguishes Slit-N polypeptides directly expressed (Specification, p.3, lines 10-19). There is no suggestion in Goodman et al. of a natural sequence Slit-N polypeptide that can be made by expressing a Slit protein in a cell, whereby the Slit protein is proteolytically processed to form the Slit-N polypeptide. Appellants are unaware of any settled legal authority holding that a product-by-process claim is not limited to a product made by the recited process.

Appellants respectfully request reversal of the pending Final Action by the Board of Appeals.

Appellants hereby petition for any necessary extension of time pursuant to 37 CFR 1.136(a). The Commissioner is hereby authorized to charge any fees or credit any overcharges relating to this communication to our Deposit Account No. 19-0750 (order no. UC99-244-2).

Respectfully submitted,
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encl. Minireview by Van Vactor et al.1999, Neuron 22, 649-652.
Goodman Declaration, 2p.

CLAIMS ON APPEAL

1. An isolated natural sequence Slit-N polypeptide.

2. A Slit-N polypeptide according to claim 1, wherein the Slit-N polypeptide is selected from the group consisting of an hSlit-1-N, an hSlit-2-N and an hSlit-3-N polypeptide.

3. A Slit-N polypeptide according to claim 1, contained in a pharmaceutical composition.

4. A Slit-N polypeptide according to claim 1, made by expressing a Slit protein in a cell, whereby the Slit protein is proteolytically processed to form the Slit-N polypeptide.

6. A pharmaceutical composition comprising a therapeutically effective amount of a Slit-N polypeptide according to claim 1, and a pharmaceutically acceptable excipient.

8. A pharmaceutical composition comprising a therapeutically effective amount of a Slit-N polypeptide according to claim 1, and a pharmaceutically acceptable excipient, further comprising a therapeutically effective amount of a neuroactive agent other than the Slit-N polypeptide.

9. A pharmaceutical composition comprising a therapeutically effective amount of a Slit-N polypeptide according to claim 1, and a pharmaceutically acceptable excipient, further comprising a therapeutically effective amount of a neuroactive agent other than the Slit-N polypeptide, wherein the agent is NGF.

12. A Slit-N polypeptide according to claim 2, contained in a pharmaceutical composition.

13. A Slit-N polypeptide according to claim 2, made by expressing a Slit protein in a cell, whereby the Slit protein is proteolytically processed to form the Slit-N polypeptide.

14. A pharmaceutical composition comprising a therapeutically effective amount of a Slit-N polypeptide according to claim 2, and a pharmaceutically acceptable excipient.

15. A pharmaceutical composition comprising a therapeutically effective amount of a Slit-N polypeptide according to claim 2, and a pharmaceutically acceptable excipient, further comprising a therapeutically effective amount of a neuroactive agent other than the Slit-N polypeptide.

16. A pharmaceutical composition comprising a therapeutically effective amount of a Slit-N polypeptide according to claim 2, and a pharmaceutically acceptable excipient, further comprising a therapeutically effective amount of a neuroactive agent other than the Slit-N polypeptide, wherein the agent is NGF.

19. A Slit-N polypeptide according to claim 1, wherein the Slit-N polypeptide is an hSlit-2-N polypeptide.

20. A Slit-N polypeptide according to claim 19, contained in a pharmaceutical composition.

21. A Slit-N polypeptide according to claim 19, made by expressing a Slit protein in a cell, whereby the Slit protein is proteolytically processed to form the Slit-N polypeptide.

22. A pharmaceutical composition comprising a therapeutically effective amount of a Slit-N polypeptide according to claim 19, and a pharmaceutically acceptable excipient.

23. A pharmaceutical composition comprising a therapeutically effective amount of a Slit-N polypeptide according to claim 19, and a pharmaceutically acceptable excipient, further comprising a therapeutically effective amount of a neuroactive agent other than the Slit-N polypeptide.

24. A pharmaceutical composition comprising a therapeutically effective amount of a Slit-N polypeptide according to claim 19, and a pharmaceutically acceptable excipient, further comprising a therapeutically effective amount of a neuroactive agent other than the Slit-N polypeptide, wherein the agent is NGF.